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LETTER TO THE EDITOR

Pantothenate kinase-associated neurodegeneration mimicking Tourette syndrome: a case report and review of the literature

Mohammad Rohani[1] · Alfonso Fasano[2,3,4] · Anthony E. Lang[2,3,4] · Babak Zamani[5] · Leila Javanparast[6] · Mohammad-Masoud Rahimi Bidgoli[6] · Afagh Alavi[6]

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Introduction

Tourette syndrome is a common neurobehavioral disorder, characterized by motor and phonic tics and various behavioral problems including attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) [1].

There is a long list of diseases causing tics and Tourettism. Huntington's disease and neuroacanthocytosis are among the most important neurodegenerative etiologies [1]. There are few case reports of neurodegeneration with brain iron accumulation (NBIA) due to presumed or genetically confirmed pantothenate kinase-associated neurodegeneration (PKAN) presenting with tics and Tourettism [2–6].

PKAN is an autosomal recessive neurodegenerative disorder caused by mutations in the *PANK2* gene [7]. The gene encodes an enzyme named pantothenate kinase 2 that is activated in the mitochondria and plays an important role in the coenzyme A (CoA) biosynthesis which is essential for production of cellular energy and lipid metabolism. Affected individuals manifest an abnormal iron accumulation in globus pallidus and the substantia nigra that leads to "eye-of-the-tiger" sign on magnetic resonance imaging (MRI) [7].

Herein, we report a case of genetically proven PKAN with Tourettism as the main clinical feature.

Case

A 13-year-old boy came to our attention due to severe motor tics. His parents were first cousins and he was the only child. According to his mother, he had a normal delivery and normal motor milestones but he had stuttering and ADHD since early childhood. Family history for tics, OCD, and other movement disorders was negative but his mother had history of ADHD. He was receiving methylphenidate for ADHD when motor tics began at the age 10. He also developed obsessive and compulsive behavior at age 12. Rarely, he uttered inappropriate words (coprolalia) without other phonic tics. He had complex motor tics such as touching and rubbing objects surrounding him. There was no history of seizures.

At the time of his first assessment, he was taking risperidone for the tics. On examination, his speech was normal. He had complex motor tics (rubbing the eyes and touching face and head, neck flexion and extension) (Video 1). On walking, there was mild dystonic posture of the toes, more severe on the right side (Video 2). The remainder of his

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✉ Afagh Alavi
afaghalavi@gmail.com; af.alavi@uswr.ac.ir

[1] Hazrat Rasool Hospital, Iran University of Medical Sciences, Tehran, Iran

[2] Edmond J. Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, University Health Network, Toronto, Ontario, Canada

[3] Division of Neurology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada

[4] Krembil Research Institute, Toronto, Ontario, Canada

[5] Department of Neurology, Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Iran

[6] Genetics Research Center, University of Social Welfare and Rehabilitation Sciences, Kodakyar Ave., Daneshjo Blvd., Evin, P.O.BOX: 1985713834, Tehran, Iran

neurologic examination was normal. Brain MRI revealed typical eye of the tiger sign (Fig. 1).

Although the clinical features were not typical of PKAN, the MRI findings encouraged us for *PANK2* mutation screening. The seven exons of *PANK 2* were amplified by polymerase chain reaction (PCR) and sequenced using ABI Big Dye terminator chemistry (Applied Biosystems, Foster City, CA). A homozygous missense mutation, c.G833T, p.Arg278Leu, was detected in the *PANK2* gene. The damaging effect of the observed variation on the encoded protein was predicted using nine different software packages (Supplementary Table 1 and Supplementary Fig. 1).

Discussion

NBIAs comprise a rare group of neurologic disorders determined by iron accumulation in the basal ganglia. PKAN is the most common form of NBIA diseases causes by mutations in *PANK2* gene. This has not been cleared how mutations in *PANK2* result in abnormal iron accumulation in the basal ganglia and specific features of the disease. It has been suggested *PANK2* mutant protein fails to fold properly and exhibits no enzymatic activity that leads to a lack of CoA biosynthesis and subsequently, an accumulation of free cysteine. This cysteine can chelate iron. Iron is highly reactive and may produce reactive oxygen species (ROS) that are destructive for lipid metabolism and may results in ROS-derived damage, impaired energy production and cell death especially in basal ganglia that naturally contains high iron content [7].

The clinical features of PKAN are diverse and extensive depending on whether it begins early (typical form) or later (atypical form) in life [7]. Among these variegated clinical features, tics and Tourettism have rarely been reported: to the best of our knowledge, there are only eight cases of PKAN and tics (Table 1) [2–6]. All of them were atypical forms of PKAN. Six patients were male and two were female. Six out of the eight were genetically confirmed with mutations in the *PANK2* gene different from the one we detected in our case; the other two patients were diagnosed clinically. All patients had eye of the tiger sign on brain MRI. Seven patients had both motor and phonic tics, one had only motor tics. In three patients, tics were the first presentation of the disease. Six patients had OCD and one had ADHD in addition to tics. All cases developed other movement disorders at presentation or during the disease course, the most prominent being dystonia.

Our case is unique since tics were the most prominent symptom and were accompanied by OCD and ADHD, as reported in only one previous case [2].

Among the other NBIA syndromes, we found one case report of neuroferritinopathy with facial tics/stereotypies. The patient was a 49-year-old man with a 2-year history of facial tics and vocalizations which were responsive to tetrabenazine [8].

We should acknowledge here that Tourette syndrome is a common movement disorder so it is possible that this case simply represents the coincidental association of a rare disease (PKAN) with a far more common disease (Tourette syndrome). On the other hand, studies show neuronal dysfunction in globus pallidus as a unit of cortico-striato-pallido-thalamic loop in patients with Tourette syndrome [9]. Thus, pathological changes in the globus pallidus of PKAN patients could readily explain the occurrence of tics and Tourettism in these patients.

In conclusion, cases mimicking, but not perfectly alike, a neurodevelopmental disorder, should be investigated further, and other possible underlying conditions such as

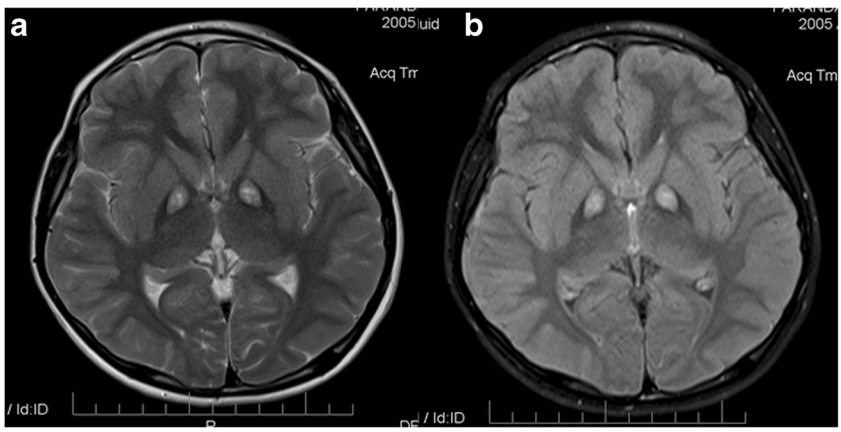

Fig. 1 Axial brain MRI showing a typical eye of the tiger on T2 and FLAIR sequences (**a** and **b** respectively)

Table 1 Clinical features and genetic analysis of reported PKAN patients with tics and Tourettism. PubMed search was performed using the terms "NBIA" OR "neurodegeneration with brain iron accumulation" OR "PKAN" OR "pantothenate kinase-associated neurodegeneration" OR "Hallervorden-Spatz syndrome" AND "tics" OR "Tourette syndrome" OR "Tourettism"

Author (year)	Sex	Age at onset (y)	Age at report (y)	Initial symptom and sign	Tics	Other neurologic signs	Other psychiatric symptoms	Brain MRI	Mutation in *PANK2*		
									DNA	Protein	Hom/Het
Nardocci et al. (1994)	M	11	17	ADHD, tics, stereotypies and compulsive behavior	Motor-phonic tics	Dystonia, gait disturbance, hypokinesia, rigidity, low IQ, gait disturbance, retinal degeneration	ADHD, OCD, impulsivity, stereotypies	Eye of the tiger	NA	NA	NA
Scarano et al. (2002)	M	10	22	Stuttering	Motor-phonic tics	Gait disturbance, rigidity, dysarthria, brisk DTRs, low IQ, dysdiadokokinesia	Impulsivity, hyperactivity	Eye of the tiger	NA	NA	NA
Pellechia et al. (2005)	M	11	26	Motor tics, behav	Motor-phonicl tics	Dysphonia, pyramidal signs, cognitive decline, gait disturbance	Behav, OCD, hyperactivity	Eye of the tiger	c.460C > T c.A635G	p.Arg154Trp p.Asp212Gly	Het
	M	16	33	Motor tics, behave and gait disturbance	Motor tics	Dystonia, rigidity, pyramidal signs, cognitive decline, retinitis pigmentosa	Behav, OCD	Eye of the tiger	c.740G > C	p.Arg247Pro	Hom
Briseno et al. (2015)	F	3	45	Gait disturbance	Motor-phonic tics	Dysarthria, Parkinsonism, hyperreflexia, cognitive decline, abnormal eye movements	OCD, aggressiveness, apathy and pseudobulbar affect	Eye of the tiger	c.1211A > T	p.Asn404Ile	Hom
	M	25	55	Gait disturbance	Motor-phonic tics	Dystonia, dysarthria, Parkinsonism, cognitive decline	OCD, aggressiveness, apathy and pseudobulbar affect	Eye of the tiger	c.1211A > T	p.Asn404Ile	Hom
	M	8	49	Dysarthria	Motor-phonic tics	Dystonia, Parkinsonism, hyperreflexia, cognitive decline	OCD	Eye of the tiger	c.1211A > T	p.Asn404Ile	Hom
Molina da Costa et al. (2016)	F	11	13	Motor-phonic tics	Motor-phonic tics	Choreathetosis, cognitive decline	Aggression, hyperactivity	Eye of the tiger	NA	NA	NA
This study	M	10	13	ADHD	Motor-phonic tics	Dystonia	ADHD, aggression, OCD	Eye of the tiger	c.G833 T	p.Arg278Leu	Hom

M male, *F* female, *NA* not available, *y* year(s), *Het* heterozygous, *Hom* homozygous, *Behav* behavior disturbance, *ADHD* attention deficit hyperactivity disorder, *OCD* obsessive-compulsive disorder, *DTR* deep tendon reflexes

PKAN have to be taken into account, before an incorrect diagnosis is drawn.

Authors contributions Mohammad Rohani: executed the study and drafted the manuscript
Alfonso Fasano: revised the manuscript for intellectual content
Anthony E Lang: revised the manuscript for intellectual content
Babk Zamani: revised the manuscript for intellectual content
Leila Javanparast: did genetic testing
Mohammad Masoud Rahimi Bidgoli:did genetic testing
Afagh Alavi: did genetic testing and revised the manuscript for intellectual content

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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